Editorial

Systemic treatment of hepatocellular carcinoma: the times they are a-changin'

Claudia Campani[1,2,3], **Jean-Charles Nault**[1,2,4,5]

[1]Centre de Recherche des Cordeliers, Sorbonne Université, Inserm, Université de Paris, Team "Functional Genomics of Solid Tumors", Paris, France; [2]Equipe labellisée Ligue Nationale Contre le Cancer, Labex OncoImmunology, Paris, France; [3]Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; [4]Service d'Hépatologie, Hôpital Avicenne, Hôpitaux Universitaires Paris-Seine-Saint-Denis, Assistance-Publique Hôpitaux de Paris, Bobigny, France; [5]Unité de Formation et de Recherche Santé Médecine et Biologie Humaine, Université Paris 13, Communauté d'Universités et Etablissements Sorbonne Paris Cité, Paris, France

Correspondence to: Jean-Charles Nault, MD, PhD. Service d'Hépatologie, Hôpital Avicenne, 125 Rue de Stalingrad, Bobigny 93000, France. Email: naultjc@gmail.com.

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For a decade, sorafenib remained the only drug approved for the treatment of advanced hepatocellular carcinoma (HCC) due to the failure of several phase III trials in which alternative angiogenesis inhibitors were tested (1). In recent years, the field of systemic treatments of HCC has evolved quickly and a recent position paper of the European Association for the Study of the Liver has well described the current advances in the systemic treatment of advanced HCC as well as the unmet needs in the field (1). First, lenvatinib was approved as an alternative to sorafenib in the first-line setting, and, thus, regorafenib, cabozantinib and ramucirumab as second-line treatments for patients who progressed on sorafenib (1). Recently, in the IMbrave150 trial, the combination of atezolizumab and bevacizumab outperformed sorafenib in terms of overall survival (OS) (19.2 *vs.* 13.4 months), progression-free survival (PFS) (6.9 *vs.* 4.3 months), objective rate response (ORR) (30% *vs.* 11%), and patient-reported outcome, and was therefore approved worldwide as the first-line standard of care for patients with unresectable HCC (1,2). In addition, in a recent phase III trial, the combination of sintilimab (anti-PD1 antibody) plus a bevacizumab-biosimilar agent obtained similar results in China (1,3). Immune checkpoint inhibitor (ICI) monotherapy has shown limited efficacy, with ORR values of 15–20% and no improvement in OS. These results may be explained by the fact that only 25% of HCCs express markers of an inflammatory response and that among these, only HCCs characterized by markers of an adaptive T-cell response are supposed to be susceptible to ICI (4). The rationale of the combination is the synergistic effect of ICIs with drugs acting on vascular endothelial growth factor (VEGF) (5). VEGF inhibitors restore normal vascularization that promote immune cell infiltration and reduce hypoxia-induced PD-L1 overexpression and the infiltration by immunosuppressive myeloid-derived suppressor and regulatory T-cells (5). Thus, the effect of ICI on activation of effector $CD8^+$ T and natural killer cells and on M1 macrophage polarization could be amplified by VEGF pathway inhibition (5). Tyrosine-kinase inhibitors (TKIs) act on multiple targets and are supposed to induce the release of cancer antigens, thus the combination of ICI and TKI could further enhance the immune response and is currently under evaluation in several clinical trials (NTC03713593, NCT03755791, NTC03418922). In the phase Ib study testing the combination of lenvatinib plus pembrolizumab, an ORR of 36–46% was reported (6).

Despite the striking efficacy of the new systemic treatments recently approved for patients with advanced HCC, Bruix *et al.* highlighted several unmet needs in the field (1). First, patient's comorbidities and treatment-related adverse event profile should be considered to select the optimal candidate to the combination of atezolizumab plus bevacizumab. Atezolizumab + bevacizumab regimen should be avoided in patients with a poorly controlled pre-

existing autoimmune disorder or when the reactivation of the disease may be life-threatening such as those targeting central nervous system or the heart (1,7).

In patients with liver transplantation, the use of ICI should be avoided because the response of such patients to the treatment can be poor due to the immunosuppressive drugs and, at the same time, the boost to the immune system can foster organ rejection (1). Sorafenib still remains the therapy of choice in liver transplanted patients for whom an advantage for second-line regorafenib has recently been suggested (8). Moreover, one of the concern on the use of atezolizumab plus bevacizumab in cirrhotic patients is related to the risk of bleeding (1). One-quarter of the patients enrolled in the combination arm of IMbrave150 trial experienced bleeding (7% gastrointestinal bleeding and 2.4% acute variceal bleeding) but it must be emphasized that the enrolled patients had optimal portal hypertension control (2,9). Patients were required to have an upper endoscopy screening for oesophageal and gastric varices within the last 6 months and those with untreated or incompletely treated varices or with high risk of bleeding were excluded (1,2). Portal hypertension, and therefore the risk of bleeding, can also worsen after the start of atezolizumab plus bevacizumab (9). Theoretically, the underling liver disease and consequently portal hypertension, can progress under the profibrogenic stimulation linked to the increase in proinflammatory cytokines and inflammatory cell recruitment induced by both anti-VEGF and immunotherapy (9). Moreover, both of these drugs have the potential to lead to sinusoidal damage that could worsen portal hypertension (9). Further research is needed to evaluate the atezolizumab-bevacizumab combination in patients with more severe portal hypertension and to establish if a personalized portal hypertension management is needed in these patients before starting the treatment. Moreover, patients with curative anticoagulation were excluded from the IMbrave150 trial and are currently excluded for treatment by atezolizumab/bevacizumab. However, more data in real life clinical practice are warranted in cirrhotic patients as bevacizumab has been used safely in other type of cancer in patients with curative anticoagulation (10).

Another question that remains unresolved is which is the best treatment option for Child-Pugh score (CPS) B patients. CPS B patients have not been enrolled in clinical trial except for nivolumab that has a good safety profile (1). In real life data, sorafenib seems tolerated in Child-Pugh B7 patients even if the impact in OS remains uncertain (11).

A recent meta-analysis of data from three phase III trials evaluating immunotherapies targeting PD1/PD-L1 pathway, showed that aetiology of the underling liver disease was linked to treatment response (12). More specifically, patients with HCC developed on non-alcoholic fatty liver disease have a shorter OS under immunotherapy (12). However, despite these results, aetiology should not be considered in the choice of treatment and further validation in prospective studies is needed (1).

The approval of atezolizumab plus bevacizumab as the new standard of care in first line setting has significant implications also on the treatment sequencing of HCC (1). All the current approved therapies have been tested in first-line or after progression on sorafenib (1). Moreover, data demonstrating the superiority of one of the current second-line treatments (regorafenib, cabozantinib, and ramucirumab) over the others are not available (and will probably not be available) (1). For these reasons, a specific therapeutic sequence is not definable and the choice of the second-line agent should be based on patient characteristics and comorbidities, safety profile and potential adverse events, health-related quality of life, and schedule of administration.

More information on the therapeutic sequency will be obtained as soon as biomarkers will be able to identify the most appropriate treatment in first and second lines. Several studies have evaluated PD-L1 expression, tumor mutational burden, aneuploidy, gene signatures, activation of the WNT and FGF pathways but none have been prospectively validated for HCC except for alpha-fetoprotein levels (>400 ng/mL) that select patients who will benefit from ramucirumab (13). Moreover, controversial data have suggested that presence of mutations of *CTNNB1* was predictive of response to immunotherapy in a mice model and in a retrospective monocentric study in HCC patients (14,15). However, prospective validation is required in order to assess the predictive value of this biomarker.

Finally, the use of tumor liver biopsy will be helpful to assess tumor molecular features and could allow the identification of the mechanism of primary and secondary resistance to systemic therapies. Therefore, the integration of tumor biopsy in future clinical trials for patients with unresectable HCC could overcome the current lack of biomarkers useful in clinical practice.

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